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## **Is lymph-node ratio a superior predictor than lymph node status for recurrence-free and overall survival in patients with head and neck squamous cell carcinoma?**

Reinisch, Sabine ; Kruse, Astrid ; Bredell, Marius ; Lübbbers, Heinz-Theo ; Gander, Thomas ; Lanzer, Martin

**Abstract:** INTRODUCTION: TNM status is questioned as an exact predictor of survival in different tumour entities. Recently, lymph node ratio (LNR) has been described as a predictor of survival in patients with HNSCC. The purpose of this study was to evaluate to which degree LNR could be used as a more accurate predictor than TNM staging? METHODS: A total of 291 patients, with a follow-up of at least 3 years, were analyzed using log-rank statistic, univariate and multivariate data analyzes, and p values, for prediction of lymph node ratio on overall and recurrence-free survival. RESULTS: Survival differed significantly if patients were stratified for LNR. Impact of LNR on survival was significantly different even in patients with extracapsular spread. Patients with pN0 had no survival benefit compared with patients with pN1 or higher with a LNR lower than 6 %. CONCLUSIONS: LNR is a prognostic tool in patients with a lymph node status pN0-pN2b. LNR remained significant even in patients with extracapsular spread, contrary to TNM status. With LNR, stratification for high-risk patients (higher than 6 % LNR) can be evaluated easily. We would suggest using LNR in the clinical routine.

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# Is Lymph-node Ratio a Superior Predictor than Lymph Node Status for Recurrence-free and Overall Survival in Patients with Head and Neck Squamous Cell Carcinoma?

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## ABSTRACT

**Introduction.** TNM status is questioned as an exact predictor of survival in different tumour entities. Recently, lymph node ratio (LNR) has been described as a predictor of survival in patients with HNSCC. The purpose of this study was to evaluate to which degree LNR could be used as a more accurate predictor than TNM staging?

**Methods.** A total of 291 patients, with a follow-up of at least 3 years, were analyzed using log-rank statistic, univariate and multivariate data analyzes, and *p* values, for prediction of lymph node ratio on overall and recurrence-free survival.

**Results.** Survival differed significantly if patients were stratified for LNR. Impact of LNR on survival was significantly different even in patients with extracapsular spread. Patients with pN0 had no survival benefit compared with patients with pN1 or higher with a LNR lower than 6 %.

**Conclusions.** LNR is a prognostic tool in patients with a lymph node status pN0–pN2b. LNR remained significant even in patients with extracapsular spread, contrary to TNM status. With LNR, stratification for high-risk patients (higher than 6 % LNR) can be evaluated easily. We would suggest using LNR in the clinical routine.

## BACKGROUND

The importance of lymph node status in head and neck squamous cell carcinoma (HNSCC) is well documented and has an important impact on recurrence-free (RFS) and overall survival (OS). The presence of even one metastatic lymph node reduces the outcome dramatically; however, this poorer survival is not expressed when looking at the prognostic value of the current TNM staging system. The search for a prognostic significance within the TNM system along with further prognostic factors is ongoing.<sup>1,2</sup>

With the introduction of lymph node ratio (LNR)—ratio between number of affected lymph nodes and number of excised lymph nodes—as a diagnostic tool in solid cancers, such as gastric, endometrioid uterine, and colorectal cancer, interest has turned to the importance of nodal ratio in oral cavity squamous cell carcinoma (OSSCC). Although there is evidence for a prognostic value in oral cavity, other regions in head and neck cancer were not investigated.<sup>3–5</sup> In a recently published paper, LNR—besides extracapsular spread—has been the only remaining independent prognostic factor in HNSCC in a multivariate analysis.<sup>6</sup>

Although tumour staging according to the American Joint Committee on Cancer (AJCC/UICC) is widely accepted, therapy regimes based on these classifications alone remain insufficient as the TNM system is based on the simplistic concept of an orderly progression of the tumour within surrounding tissues, then transgressing lymphatic and vascular barriers. Evidence of a more complex system is evolving leading to many other prognostic parameters being investigated.<sup>1,2</sup> Urban et al.<sup>7</sup> have demonstrated the importance of LNR to estimate the benefit of postoperative radiotherapy in oral cavity cancer.

**Conduction of Study** Patient data derived from patients treated at the University Hospital of Graz (1). The study was approved by the Institutional Ethics Committee (EK-Nr. 21-020 ex 09/10).

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Association between LNR and lymph node staging does currently not exist.

The study purpose is to address the following questions: is LNR among patients with HNSCC, a more valid prognostic factor for recurrence-free and overall survival than TNM staging system; does this evidence valid for other regions than the oral cavity in HNSCC; and to what extent is LNR a tool for treatment decisions? Hypothesis of this study is that LNR, if merged with tumour lymph node staging, offers a more precise predictor for recurrence-free and overall survival, in patients with HNSCC than mere nodal stage as a single factor.

To compare the relation between lymph node staging and LNR, we looked at each aspect separately followed by merging of the LNR and lymph node staging to evaluate diversity between those two prognostic factors.

## MATERIALS AND METHODS

### *Study Design*

We developed a retrospective patient database for patients who underwent primary surgery including neck dissection for head and neck squamous cell carcinoma.

### *Study Sample*

The study population was derived from patients who presented at the Department of Otorhinolaryngology and Head and Neck (ENT) at the Medical University Hospital Graz for treatment of HNSCC between 1 January 1999 and 31 December 2009. Of 465 patients, 291 met the criteria. The study was approved by the institutional ethics committee.

Inclusion criteria were a diagnosis of HNSCC and operative treatment at the primary tumor site with or without adjuvant radiotherapy or radiochemotherapy. Subjects were excluded if they had histological findings other than SCC, distant metastasis before neck dissection (ND), or were treated primarily outside the ENT department. Follow-up of patients had to be documented for at least 3 years.

Patients were treated by resection of the primary tumour combined with uni- or bilateral ND. Because this is a retrospective data collection, we cannot validate the indication of the ND but can characterize them as radical, standardized modified radical, or selective (supraomohyoid, lateral, posterolateral) as described by the American Head and Neck Society.<sup>8</sup> (Starting point of this study was before 2001, therefore the Classification of 1991 was used.)

### *Study Variables*

Variables examined were: age and sex; tumor location, stage, size, and grade; neck lymph node status; histological

factors [vascular—(hemangiosis), lymphatic—(lymphangiosis), perineural invasion, extracapsular spread of lymph nodes, conglomerate lymph nodes]; resection margin; number of positive lymph nodes; LNR and use of adjuvant therapy (postoperative chemotherapy and/or adjuvant radiotherapy).

### *Points of Interest*

Univariate analysis was used to identify factors significantly affecting RFS and OS, and multivariate analyses of significant factors was used to identify independent prognostic factors.

### *Data Collection, Management, and Analyses*

Data were collected and processed by building a database of information about the patient (sex, age), tumour (location, size, lymph node status), surgery (date, type of resection, resection margin, type of ND, number of levels excised, number of lymph nodes excised, number of positive lymph nodes, excision of non lymphatic structures), histopathological diagnostic findings (hemangiosis, lymphangiosis, extracapsular spread, perineural invasion), postoperative therapy, second primary tumours, location and time of recurrence, and OS. Patient data were analyzed using SPSS software (SPSS Inc., Chicago, IL).

Descriptive statistics were computed for each variable. Univariate Cox regression analysis was used for each variable, and odds ratios and *p* values were calculated. Multivariate Cox regression analysis was used for each predictor variable ( $p < 0.05$ ) identified as significant in univariate analysis. We used a forward step-wise (likelihood ratio) procedure.

For the analysis of cutoff points for LNR, the “maximally selected rank statistic” method of Lausen and Schumacher<sup>9</sup> was used. Cutoff points with the highest diversity of groups were calculated.

## RESULTS

In total, 291 patients were included (Table 1). The mean age was 64 (range, 27–87) years. Most (82.8 %) patients were men. The mean follow-up duration was 38 months (maximum, 128 months). Most patients had a tumour in the oropharyngeal region (32 %), followed by the oral cavity (25.4 %), hypopharynx (16.8 %), larynx (15.1 %), unknown primary location (8.6 %), and nasopharynx (2.1 %). Most patients presented with a stage IV tumour (56 %), followed by stage III (19.6 %), stage II (13.7 %), and stage I (10.7 %). Regarding T-status, most patients presented with a T2 tumour (29.4 %). Lymph node status

**TABLE 1** Descriptive statistics of 291 patients

	Attribute	Number	Percentage	Mean	SD	Median	Minimum	Maximum
Age [in years]		291		64.08	10.6	64	27	87
Follow-up [mo]		291		38.39	32.6	27.2	0.1	128.3
Sex	Male	241	82.8					
Localization	Oral cavity	74	25.4					
	Oropharynx	93	32					
	Nasopharynx	6	2.1					
	Hypopharynx	49	16.8					
	Larynx	44	15.1					
	Unknown primary	25	8.6					
TNM stage	Stage I–II	71	24.4					
	Stage III–IV	220	75.6					
Tumor stage	T1-2	150	51.6					
	T3-4	116	39.9					
	Tx	25	8.6					
Lymph node status	N0	109	37.5					
	N1	38	13.1					
	N2a	28	9.6					
	N2b	90	30.9					
	N2c	15	5.2					
	N3	11	3.8					
Tumor grade	Well/moderately differentiated	137	47					
	Poorly/undifferentiated	154	52.9					
Perineural invasion	No	268	92.1					
	Yes	23	7.9					
Lymphangiosis	No	270	92.8					
	Yes	21	7.2					
Hemangiosis	No	284	97.6					
	Yes	7	2.4					
Capsule penetration	No	237	81.4					
	Yes	54	18.6					
Conglomerate lymph nodes	No	261	89.7					
	Yes	30	10.3					
Resection margin	Negative	228	78.4					
	Positive	63	21.6					
Number of positive lymph nodes	0	109	37.5					
	1	77	26.5					
	2–5	77	26.5					
	>5	28	9.6					
Lymph node ratio	0–6 %	187	64.3					
	>6–13 %	48	16.5					
	>13 %	56	19.2					
Lymph node ratio (pos/exc) [%]		291		8.04	13.0	3.7	0	100
Adjuvant therapy	No	113	38.8					
	Radiotherapy	140	48.1					
	Chemotherapy	1	0.3					
	Radiochemotherapy	37	12.7					

SD standard deviation

was pN0 in 37.5 % of patients, followed by pN2b in nearly 31 % of patients. Because patients with distant metastasis at diagnosis were excluded, all patients were in the M0 state.

Tumour grade was dominated by patients with moderately (43.6 %) or poorly (51.2 %) differentiated tumours. Only a few patients presented with well-differentiated or undifferentiated tumours. Perineural invasion was seen in 7.9 % of patients; the percentage of lymphangiosis, hemangiosis, extracapsular spread, and conglomerate lymph nodes was 7.2, 2.4, 18.6, and 10.3 %, respectively.

Operative success, defined as a negative resection margin by at least 5 mm (R0 resection), was achieved in 78.4 % of patients. R1 resection was achieved in 19.9 % of patients and tumour resection was macroscopically positive (R2 resection) in five (1.7 %) patients. Forty-one (14.1 %) patients underwent radical ND. The largest proportion of patients was treated with modified radical ND (28.9 %), followed by supraomohyoid (26.3 %), posterolateral (25.1 %), and lateral selective (5.5 %) NDs.

In 66 patients, an additional selective contralateral neck dissection of one level was conducted, if there were suspected lymph nodes contralaterally. The mean number of lymph nodes removed was 27 lymph nodes in total. Most patients had a lymph node status higher than N1 (pN2) and a lymph node density of 0–6 % (183 patients).

Results of neck dissections demonstrated a pN0 situation in 37.5 % of patients. One or 2–5 lymph nodes were positive in 26.5 % in both groups. In 9.6 % of patients, more than five lymph nodes were affected. Nearly two-thirds of patients (187) had LNR between 0 and 6 %. A LNR of >6–13 % was documented in 48 patients, and a LNR higher than 13 % in 56 patients. In total, 113 (39.2 %) patients received no adjuvant therapy, 140 (48.1 %) patients received radiotherapy, 37 (12.7 %) received combined radiochemotherapy, and 1 patient received chemotherapy alone.

Two-thirds of patients (193) experienced no recurrence during follow-up. Recurrence was observed in 98 (33.7 %) cases; distant metastasis occurred in 34 % of these patients.

Both, RFS and OS differed significantly if patients were stratified for LNR. Log-rank test was  $p < 0.001$  for RFS (Fig. 1) and OS (Fig. 2), each. RFS and OS remained significant considering LNR if only patients with a pN2a and pN2b were included in analysis (Fig. 2). LNR 0–6 % had a significant favourable prognosis compared to LNR higher than 6 % in those patients, with a  $p$ -value of 0.009 and  $>0.001$  for RFS and OS, respectively. Only seven patients with a pN1 had a LNR of higher than 6 %; therefore, comparison of RFS and OS in these patients could not be sufficiently evaluated, and statistics were not valid.

If survival curve of patients with a negative neck were compared to patients with a positive neck and a lymph

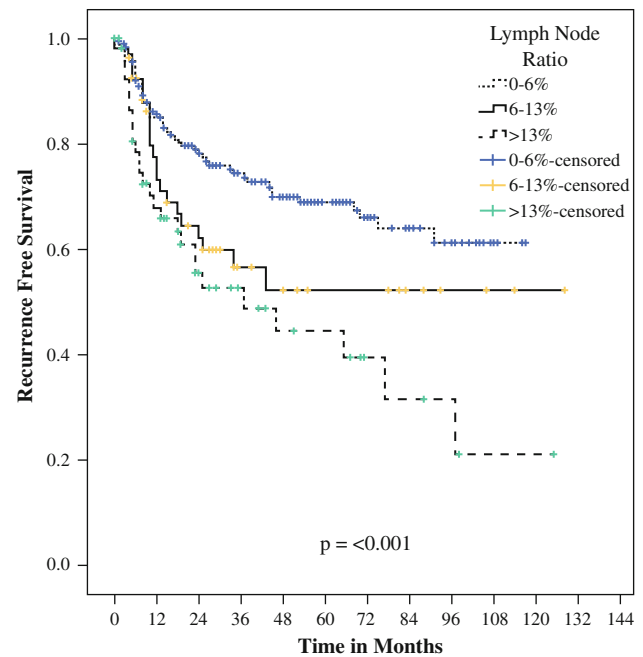


FIG. 1 Recurrence free survival considering lymph node ratio

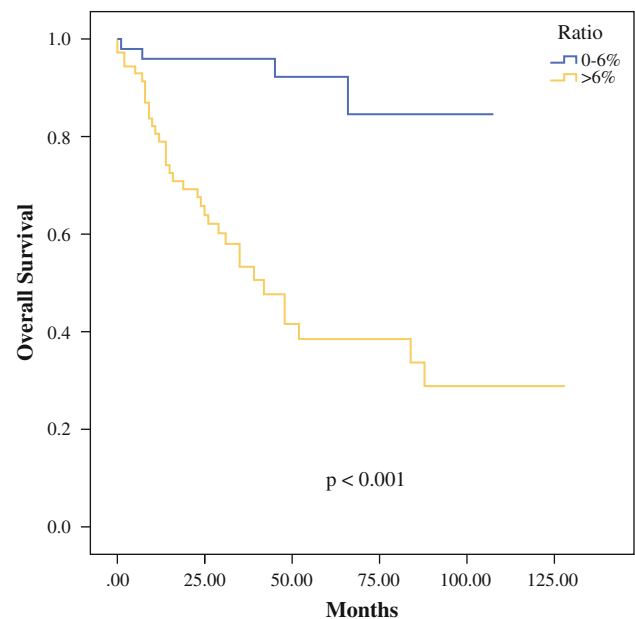
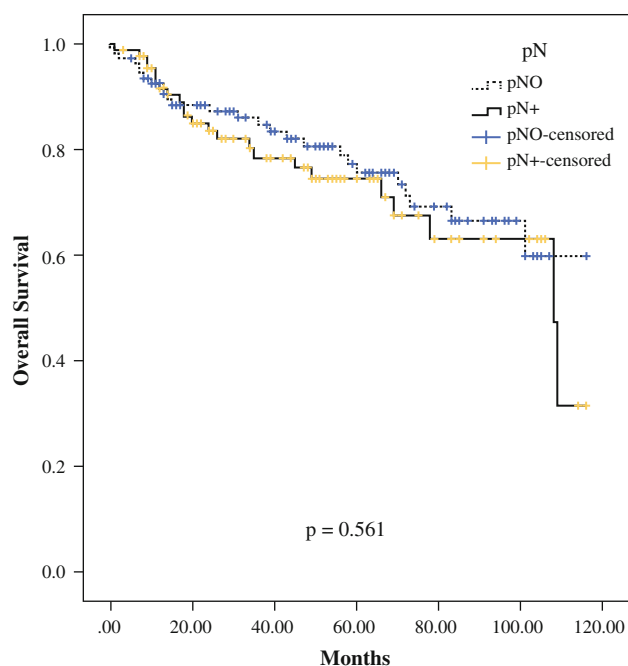


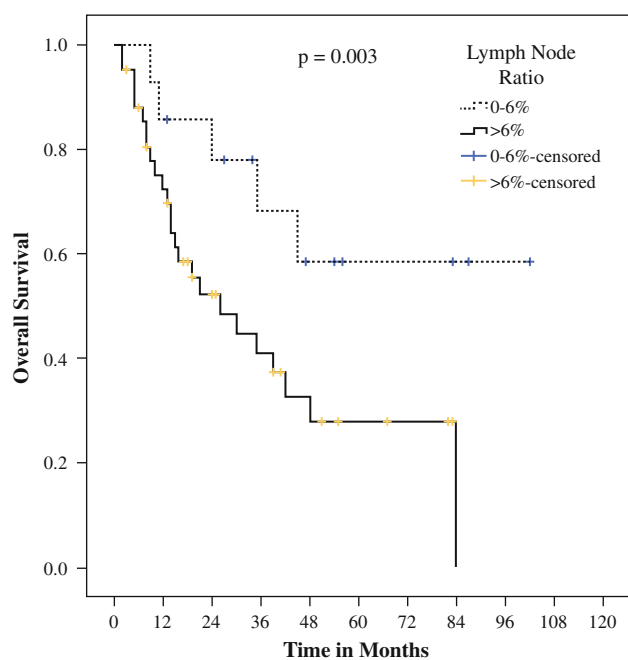
FIG. 2 Overall survival depending of lymph node ratio in patients with a pN2a or pN2b status

node ratio 0–6 %, there was no difference in run of curves. Log-rank test was not significant at  $p = 0.561$  (Fig. 3).

In patients with extracapsular spread, RFS was not significant considering LNR. However, impact of lymph node ratio on OS was significantly different even in patients with extracapsular spread ( $p = 0.003$ ) (Fig. 4). There was no significant difference in RFS and OS of patients without extracapsular spread after data was stratified for TNM status.



**FIG. 3** Overall survival in patients with a pN0 or pN+ status if LNR is 0–6 % in patients with pN+



**FIG. 4** Overall survival in patients with extracapsular spread

When the number of positive lymph nodes is considered as sole factor, RFS and OS differed significantly if 0, 1, 2–5, or more than five lymph nodes were affected. *P* value for RFS and OS was 0.004 and <0.001, respectively. However, if numbers of lymph nodes were stratified with lymph node ratio, numbers of affected lymph nodes were not significant any more.

Lymph node ratio remained a significant factor for RFS and OS even if postoperative radiotherapy was applied ( $p = 0.005$  for each); however, no significance was detected if radiochemotherapy was applied postoperatively as adjuvant therapy.

## DISCUSSION

It is advocated that the absence/presence of cervical lymph node metastases is the most important prognostic factor in HNSCC. The challenge is to evaluate accurately the prognostic impact of positive cervical lymph nodes, because N-classification does not predict tumour-free survival.<sup>10</sup>

Among OSCC patients with positive neck nodes, Shingaki et al.<sup>11</sup> proposed that nodal classification may not necessarily predict prognosis. Descriptive TNM staging cannot be used as survival predictive tool if not combined with other descriptive prognostic factors, such as extracapsular spread, tumour infiltration, biomarkers to further predict the biologic behaviour of an individual tumour, and last but not least surgical success. In other tumour sites, TNM status also is questioned as an exact predictor of survival. Lymph-node ratio (LNR) has been described as a predictor of survival in patients with head and neck squamous cell carcinoma. Furthermore, LNR is described to be superior to TNM nodal status in patients with bladder cancer.<sup>12, 13</sup> Ooki et al.<sup>14</sup> described the prognostic benefit of LNR over TNM in advanced oesophageal squamous cell carcinoma. In this article, lymph node ratio is evaluated regarding its power for RFS and OS prediction.

Clayman et al.<sup>15</sup> confounded lymph node levels at highest risk for lymph node metastasis and set recommendations of selective procedure for every tumour site in patients with HNSCC. This hypothesis is supported by Patel et al.<sup>16</sup> and Shepard et al.<sup>17</sup> who could not find a significant benefit of comprehensive neck dissection versus selective neck dissection for locoregional recurrence-free survival. With the knowledge of lymph node levels most likely at risk for each tumour entity, and the reassurance that a radical neck dissection is not superior to selective procedures by the literature mentioned, LNR could be a safety net along the way of selective lymph node surgery.

It is suggested that number of lymph nodes differ between tumour patients and healthy people.<sup>18</sup> Beasley et al.<sup>19</sup> demonstrated intratumoral lymphogenesis by using a lymphatic endothelial marker, LYVE-1. Others described an increased lymph vessel density in patients with oropharyngeal cancer.<sup>20</sup> Hence, it is assumed that lymphatic tumour spread is supported by tumour-associated lymphogenesis and numbers of excised lymph nodes during neck dissection may be of importance to evaluate its potential for lymphogenesis and may be a reflection of tumour biology characteristics.



Patients with a single positive lymph node (pN1 or pN2a) would benefit from lymph node ratio as a predictive factor, for example in case of a diagnostic lymph node dissection that happens to be one single positive lymph node associated with an unfavourable LNR. According to the LNR the patient may be offered an extension of his ND to improve disease-specific survival. With the use of LNR, underestimation of the neck situation might be prevented.

Patients with more than one positive ipsilateral lymph node would benefit from LNR, because locoregional tumour spread could be evaluated. For example, if two lymph nodes are affected and a large number of excised lymph nodes around those affected nodes are tumour-free the possibility of metastasis to other areas is less likely, similarly if metastasis of level 5 is present in absence of involvement of levels 4 or 3.<sup>21</sup> On the contrary, if a comprehensive neck dissection delivers wide spread nodal metastasis, distant metastasis is more likely to occur and therefore additional treatment has to be considered.

Two situations should be mentioned where LNR cannot be regarded as a diagnostic tool: (1) in case of lymph node metastasis to the contralateral neck (pN2c); and (2) if one or more lymph nodes are larger than 6 cm (N3) in diameter. In case of pN2c, LNR is not valid, due to locoregional tumour spread to the contralateral side; therefore, a bilateral comprehensive neck dissection would be necessary to use lymph node ratio for prediction. Likewise, in patients with pN3, clear differentiation between one single lymph node bigger than 6 cm or a conglomerate of smaller lymph nodes often is not possible.

Importance of extracapsular tumour spread in patients with HNSCC is well documented in the literature.<sup>22</sup> Data of this study could demonstrate the validity of LNR even in patients with extracapsular spread. A “surrounding wall” or effective biologic barrier of not affected lymph nodes seems to play a role in preventing distant metastasis.

According to the presented data—with the limitation of a retrospective data analysis—LNR cannot only be used to evaluate the effectiveness of the surgery, but also implicate further therapies. Importance of LNR for decision making towards adjuvant therapy seems to be a highly accurate question that needs support by further prospective studies on this issue. Unfavourable high lymph node ratio (>6 %) should undergo further comprehensive surgery (if this was not the case in first place) or be treated with adjuvant therapy. The data presented demonstrated the unfavourable prognosis of high lymph node ratio if solely radiotherapy was applied. In combined postoperative treatment (radiochemotherapy), RFS and OS did not differ. However, the indication that patients with higher LNR should be treated with radiochemotherapy should be taken with precaution, because the number of patients in this subgroup was only 37, thus limiting the statistical significance.

Some patients, especially in case of a pN2a status, might be treated sufficiently by neck dissection only—with the benefit of patient comfort, morbidity, and the chance of radiotherapy in case of a recurrence—because of a benign lymph node ratio.

In conclusion, is the hypothesis of whether LNR is superior than TNM evaluated? In patients with a positive lymph node status, but a lymph node ratio of 0–6 %, we could demonstrate that RFS and OS did not differ comparing to patients with a negative lymph node status. We could demonstrate the significant difference in predicting RFS and OS in patients with a pN2a and pN2b status after stratifying lymph node ratio. Lymph node ratio remained significant in patients with an extracapsular spread—contrary to TNM status. Therefore, we suggest that LNR is used as a predictor for survival in patients with an affected ipsilateral neck. If contralateral neck is affected and/or lymph nodes are a conglomerate, lymph node ratio is not valid.

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**CONFLICT OF INTEREST** Authors declare no conflict of interest.

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